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| EXAMINER | |
|---|---|
| SISSON, BRADLEY L | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/533,847 | URNOV ET AL. | |
| | Examiner | Art Unit | |
| | Bradley L. Sisson | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1 and 6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 May 2008 has been entered.

### *Election/Restrictions*

2. Claims 1 and 6-15 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01 August 2007.

3. This application contains claims 1 and 6-15, drawn to an invention nonelected with traverse in the reply filed on 01 August 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Priority***

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in United States of America on 17 November 2003. It is noted, however, that applicant has not filed a certified copy of the PCT/US03/37044 application as required by 35 U.S.C. 119(b).

***Drawings***

5. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

a. The lettering is not of proper size, uniform density, and well-defined in Figure(s) Figs. 105;

b. The lines are not clean, well-defined, and of uniform thickness in Figure(s) 1-5;

c. Each panel needs to be individually labeled, e.g., Fig. Figure 2a-Figure 2D,

6. Attention is directed to the following section of 37 CFR 1.84.

(c) *Identification of drawings.* Identifying indicia should be provided, and if provided, should include the title of the invention, inventor 's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet within the top margin. Each drawing sheet submitted after the filing date of an application must be identified as either "Replacement Sheet" or "New Sheet" pursuant to § 1.121(d). If a marked-up copy of any amended drawing figure including annotations indicating the changes made is filed, such marked-up copy must be clearly labeled as "Annotated Sheet " pursuant to § 1.121(d)(1).

(g) *Margins.* The sheets must not contain frames around the sight ( i.e., the usable surface), but should have scan target points ( i.e., cross-hairs) printed on two cater-corner margin corners. Each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5 /8 inch), and a bottom margin of at least 1.0 cm. (3 /8 inch), thereby leaving a sight no greater than 17.0 cm. by 26.2 cm. on 21.0 cm. by 29.7 cm. (DIN size A4) drawing sheets, and a sight no greater than 17.6 cm. by 24.4 cm. (6 15 /16 by 9 5 /8 inches) on 21.6 cm. by 27.9 cm. (8 1 /2 by 11 inch) drawing sheets.

(l) *Character of lines, numbers, and letters.* All drawings must be made by a process which will give them satisfactory reproduction characteristics. Every line, number, and letter must be durable, clean, black (except for color drawings), sufficiently dense and dark, and uniformly thick and well-defined. The weight of all lines and letters must be heavy enough to permit adequate reproduction. This requirement applies to all lines however fine, to shading, and to lines representing cut surfaces in sectional views. Lines and strokes of different thicknesses may be used in the same drawing where different thicknesses have a different meaning.

(m) *Shading.* The use of shading in views is encouraged if it aids in understanding the invention and if it does not reduce legibility. Shading is used to indicate the surface or shape of spherical, cylindrical, and conical elements of an object. Flat parts may also be lightly shaded. Such shading is preferred in the case of parts shown in perspective, but not for cross sections. See paragraph (h)(3) of this section. Spaced lines for shading are preferred. These lines must be thin, as few in number as practicable, and they must contrast with the rest of the drawings. As a substitute for shading, heavy lines on the shade side of objects can be used except where they superimpose on each other or obscure reference characters. Light should come from the upper left corner at an angle of 45 °. Surface delineations should preferably be shown by proper shading. Solid black shading areas are not permitted, except when used to represent bar graphs or color.

(n) *Symbols.* Graphical drawing symbols may be used for conventional elements when appropriate. The elements for which such symbols and labeled representations are used must be adequately identified in the specification. Known devices should be illustrated by symbols which have a universally recognized conventional meaning and are generally accepted in the art. Other symbols which are not universally recognized may be used, subject to approval by the Office, if they are not likely to be confused with existing conventional symbols, and if they are readily identifiable.
(o) *Legends.* Suitable descriptive legends may be used subject to approval by the Office, or may be required by the examiner where necessary for understanding of the drawing. They should contain as few words as possible.

(p) *Numbers, letters, and reference characters.*
(1) Reference characters (numerals are preferred), sheet numbers, and view numbers must be plain and legible, and must not be used in association with brackets or inverted commas, or enclosed within outlines, e.g., encircled. They must be oriented in the same direction as the view so as to avoid having to rotate the sheet. Reference characters should be arranged to follow the profile of the object depicted.
(2) The English alphabet must be used for letters, except where another alphabet is customarily used, such as the Greek alphabet to indicate angles, wavelengths, and mathematical formulas.

> (3) Numbers, letters, and reference characters must measure at least .32 cm. (1/8 inch) in height. They should not be placed in the drawing so as to interfere with its comprehension. Therefore, they should not cross or mingle with the lines. They should not be placed upon hatched or shaded surfaces. When necessary, such as indicating a surface or cross section, a reference character may be underlined and a blank space may be left in the hatching or shading where the character occurs so that it appears distinct.

7. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

**INFORMATION ON HOW TO EFFECT DRAWING CHANGES**

**Replacement Drawing Sheets**

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

**Annotated Drawing Sheets**

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

**Timing of Corrections**

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 2-5 are all drawn to an array, which comprises sequences that correspond to accessible regions of cellular chromatin, and are isolated based on their altered activity to probe of chromatin structure. A review of the disclosure finds that a Sequence Listing was filed on 17 November 2005. Said Sequence Listing, however, has been found to comprise but a single sequence, and then the sequence depicted is that of 25 amino acids of an indeterminate composition, not of multiple nucleic acids that are derived from "accessible regions of cellular chromatin and are isolated based on their altered reactivity to probe of chromatin structure." For convenience, the sole disclosed sequence is reproduced below.

```
<400> SEQUENCE: 1
      Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      1               5                  10                  15
      Xaa Xaa His Xaa Xaa Xaa Xaa Xaa His
                  20                  25
```

10. While the claimed invention is defined in terms of the process used to isolate it, and not in terms of its nucleotide structure, the specification similarly fails to describe the composition of the probe(s) that are used to isolate the members of the array.

11. As presently worded, the claimed array can comprise "available" nucleic acids that are derived from any life form as well as variants of same. In support of this position, attention is directed to page 8, last paragraph, of the specification, which states in part:

> Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated.

12. A review of the disclosure fails to find where any array of any nucleic acids has been prepared, regardless of the accessibility of the nucleotide sequence.

13. For purposes of examination, the array of polynucleotide sequences has been construed as encompassing at the very least, two nucleic acids molecules. A review of the disclosure has fails to identify where applicant has prepared any array, including an array that has two nucleic acids molecules, be they accessible or not.

14. While the specification explicitly allows for the inclusion of variants, the specification has not been found to provide an adequate written description of those nucleic acid molecules that are useful versus those that are not.

15. The absence of an adequate written description for any such array does not reasonably suggest that applicant had possession of the array at the times of filing.

16. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

17. For the above reasons, and in the absence of convincing evidence to the contrary, claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

18. Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

19. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' "Genentech, *Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice

> a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary

The quantity of experimentation necessary is great, on the order of several man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims.

The amount of direction or guidance presented,

The amount of guidance provided is limited, generally prophetic, and not commensurate with the scope of the claims. The specification does not set forth any array, much les a method of using same.

The presence or absence of working examples

The specification comprises the following examples:

Example 1: Preparation of regulatory DNA library from HEK 293 cells, pp. 61-62. In this example, total nuclear DNA was isolated, restricted, and inserted into a plasmid. Applicant reports that 40,000 – 50,000 clones were obtained.

Example 2, Analysis of Selected Clones, pp. 62-66. 1% of he clones from Ex. 1 were evaluated.

Example 3: Identification of target sequences of Estrogen Receptor (ER), pp. 66-67; and

Example 4: Analysis of Drug Effects, pp. 67-68. DNA from estrogen treated and untreated cells were hybridized to regDNA chips. The composition, source and manner of making the chips are not disclosed.

None of the examples is directed to the identification of nucleic acid molecules that corresponds to accessible regions of cellular chromatin and is isolated based on their altered reactivity to probe of chromatin structure, and which are each individually isolated and bound to a distinct address on a solid support.

It is further noted that none of the examples teach how the claimed array is to be used in a method that has utility. While the elected invention is drawn to an array and not to a method of use, the specification must still enable the making and use of the invention. In the present case, the specification has not been found to do either. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****

> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
>
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

The nature of the invention and the breadth of the claims

The invention relates generally to arrays of nucleic acids where each nucleotide sequence is located at a distinct address on a solid support. The nucleic acids are characterized in that they correspond to accessible regions of cellular chromatin and are isolated based on an unspecified altered reactivity to probing of chromatin structure.

The members of the array can be of virtually any length, and at any density.

The array fairly encompasses nucleic acids that are derived from any life form.

The state of the prior art and t he predictability or unpredictability of the art

The art to which the invention relates, i.e., nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

> While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature ($0.97^{25}$ to $0.99^{25}$). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.
>
> Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long ($0.90^{25}$ to $0.95^{25}$).

At column 40 of Jones (US Patent 5,858,671) the inherent obstacle in synthesizing oligonucleotide arrays is disclosed. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a

99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69} = 0.50$)." In the present case, applicant is claiming a product that would be the result of an infinite number of couplings, not just 69 as described above.

As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

20. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

21. Claims 2-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

22. It is noted with particularity that the claimed array is defined in terms of a product-by-process. While such claim format is permissible, the claim must still be directed to a product that has utility. However, not al nucleic acids have utility. An example of such are expressed sequence tags (ESTs) for which no known utility exists. The claimed array does not differentiate between those nucleic acids that do and do not have utility.

23. Acknowledgement is made of where applicant has provided a listing of potential utilities at page 53 of the specification. Such asserted utilities are not deemed to be specific to the members of the array.

24. It matters not whether the claim is drawn to a product or process; the claim must be drawn to an invention that satisfies the utility requirements as set forth under 35 USC 101 and as further developed in the Utility Guidelines. In support of this position, attention is directed to *Brenner, Comr. Pats. v. Manso*n, 148 USPQ 689 (US Sup Ct 1966):

> Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, 22 without compensating benefit to the public. The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> * * *
>
> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product. 24 That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.
> This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of the invention of something "useful," or that we are blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

25. Claims 2-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

26. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

28. Claims 2-5 are indefinite as a result of the use of the term "sequences." It would appear that applicant is referring to >>polynucleotides<< or to >>nucleotide sequences<<.

29. Claims 2-5 are indefinite with respect to what constitutes the metes and bounds of "accessible regions." Acknowledgement is made of the definition found at page 12, last paragraph, of the disclosure. The use of modifiers or qualifiers in the definition has rendered same non-limiting. Accordingly, the metes and bounds of the claims cannot be readily determined. It is further noted that applicant' representative directs attention to those that may not have "typical nucleosomal structure." The specification, however, ahs not been found to set forth a definition of what constitutes "typical nucleosomal structure."

30. Claims 2-5 are indefinite as a result of the expression "are isolated based on their altered reactivity to probe of chromatin structure" (emphasis added).

***Claim Rejections - 35 USC § 102/103***

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

34. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35. Claims 5-6 are product-by-process claims. Guidance as to the examination of such claims are addressed under MPEP 2113 [R-1], which for convenience, is reproduced below.

**2113 [R-1] Product-by-Process Claims**

**PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS**

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

>The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded," "intermixed," "ground in place," "press fitted," and "etched" are capable of construction as structural limitations.)<

**ONCE A PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS FOUND AND A 35 U.S.C. 102 /103 REJECTION MADE, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE**

"The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983) (The claims were directed to a zeolite manufactured by mixing together various inorganic materials in solution and heating the resultant gel to form a crystalline metal silicate essentially free of alkali metal. The prior art described a process of making a zeolite which, after ion exchange to remove alkali metal, appeared to be "essentially free of alkali metal." The court upheld the rejection because the applicant had not come forward with any evidence that the prior art was not "essentially free of alkali metal" and therefore a different and unobvious product.). Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. &

Inter. 1989) (The prior art disclosed human nerve growth factor (b-NGF) isolated from human placental tissue. The claim was directed to b-NGF produced through genetic engineering techniques. The factor produced seemed to be substantially the same whether isolated from tissue or produced through genetic engineering. While the applicant questioned the purity of the prior art factor, no concrete evidence of an unobvious difference was presented. The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art. The Board further stated that the applicant should have made some comparison between the two factors to establish unexpected properties since the materials appeared to be identical or only slightly different.).

**THE USE OF 35 U.S.C. 102 /103 REJECTIONS FOR PRODUCT-BY-PROCESS CLAIMS HAS BEEN APPROVED BY THE COURTS**

"[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

36. Claims 2-5 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 5,474,796 (Brennan).

37. While the claims recite that the nucleic acid is to be "isolated based upon their altered reactivity to probe of chromatin structure," the conditions, and degree of "altered activity" is without limit. It is further noted that the array can comprise variants. In support of this position, attention is directed to page 8, last paragraph, of the specification, which states in part:

> Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated.

38. It is further noted that the claim employs the term "comprises." Such language opens up the claim to include additional ingredients or elements, even in significant amounts.

39. Brennan, column 9, discloses an array of oligonucleotides that comprises all possible 10-mers. Each of these oligonucleotides occupies a distinct address on the support. Such a showing is deemed to meet a limitation of claims 2-5.

40. While claims 2-5 have been drafted in terms of a product-by-process, there is no structural difference from the polynucleotides of the array of Brennan from that claimed instantly.

41. At page 10 of the response of 12 May 2008, argument is presented:

> By contrast, the oligos of Brennan's arrays do not consist of sequences corresponding to accessible regions. It is nonsensical to assert that arrays including all possible 10-mers are necessarily sequences "corresponding to" accessible regions on the grounds that these 10-mers do not have a typical nucleosome structure. The fact remains that both arrays will have naked DNA, but only in the claimed arrays will each and every sequence correspond to a sequence of an accessible region. Simply put, the claimed arrays and Brennan's arrays are, by any definition, different arrays.

42. As an initial matter, the claims do not recite any language concerning "typical nucleosome structure." Further, the specification explicitly allows for the inclusion of variants. And as also noted above, the claims fairly encompass the use of virtually any conditions in establishing just what constitutes "altered reactivity to probe of chromatin structure." In short, the absence of limiting definition fairly opens the claims up to where they encompass virtually any and all manner of nucleic acids.

43. Accordingly, and in the absence of convincing evidence to the contrary, claims 2-5 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,474,796 (Brennan).

***Conclusion***

44. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

45. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

46. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634